ON CHANGES IN THE CENTRAL NERVOUS SYSTEM IN THE NEURITIC DISORDERS OF CHRONIC ALCOHOLISM.[1]

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It is now well known that in alcoholic paralysis, as in other forms of toxic neuritis, the degeneration of peripheral nerve-fibres does not stand alone, but is associated with a more or less characteristic type of change in the related nerve-cells. Moreover, in recent years observations have been reported which tend to show that this combination of fibre degeneration with cell change is, at least in many acute cases of the disease, not confined to neurones which go to make up peripheral nerves, but is exhibited also by neurones of various groups situated entirely within the brain and cord. The disease is something more than a mere peripheral neuritis, and represents a very wide-spread affection of the whole nervous system. Not only does it appear to be allied to certain spinal degenerations, but it stands in intimate clinical and pathological relationship with a number of important cerebral disorders in which there may be no appreciable peripheral affection.

During three years in which I was a medical officer at Colney Hatch Asylum, there came under my observation fifteen cases of alcoholic neuritis, and in three of these I had an opportunity of making a pathological examination. The observations are here recorded. A more detailed account of case 1 will shortly appear, with illustrations, in vol. ii. of the "Archives of Neurology" of the London County

[1] Abridged and adapted from a thesis for the Oxford M.D. degree.

Asylums. A comparative study of that case with the two others subsequently investigated, is however of sufficient interest to induce me here to give a brief abstract of it. For the three cases present not only important resemblances, but also instructive differences, so that much of their significance becomes apparent only when they are examined side by side.

The observations here recorded suggest: (1) That the peripheral and central lesions express a nervous degeneration of toxic origin, in the production of which no essential part is played by changes in interstitial tissues supporting the nervous structures, or by changes in the blood vessels concerned with their nutrition. (2) The changes in the nerve-cells are not the mere result of antecedent damage of nerve-fibres, but the changes in the fibres and cells together express a highly selective affection of whole neurones. (3) The peripheral neuritis is simply a local expression of this affection, and is not of purely local and peripheral causation. (4) The lesion of peripheral neurones is only one of many manifestations of the disease, and is accompanied by lesions identical in nature, affecting many groups of neurones situated entirely within the central nervous system. (5) The central changes are not attributable to the peripheral neuritis, and though in some cases the peripheral neurones are mainly affected, in others the morbid process chiefly implicates central neurones; but these two groups of cases do not appear to be sharply divided.

CASE 1.—*Acute alcoholic paralysis, fatal after six weeks duration, and presenting all the usual clinical and pathological evidences of acute degeneration of cranial and spinal nerves. "Polyneuritic" mental disorder. Death from vagus paralysis and heart failure. No appreciable vascular changes in nervous system. Acute cell changes in cord, spinal ganglia, medulla and cortex. Degeneration of pyramidal tracts, fronto-thalamic fibres, and the exogenous fibres of the posterior columns.*

Well-developed, well-nourished woman, aged 32, married. History of eight years' excessive gin-drinking; several attacks of delirium tremens; brief mania a potu with suicidal and homicidal

impulses, July, 1898. Admitted to Colney Hatch, September 7, 1900, five weeks after sudden onset of acute multiple neuritis. Mental confusion, defective ideas as to time and place, loss of memory for recent impressions, delusion of recent confinement, and illusions as to identity of persons around her.

Complete paralysis of legs, with complete anæsthesia and analgesia, wasting of muscles and loss of reaction to faradism, and foot-drop; trophic blisters on heel and malleolus. Wasting of upper limb muscles, with marked weakness, especially of extensors; wrist-drop; diminution of faradic excitability; slight impairment of cutaneous sensation on forearms and hands without analgesia. Cutaneous sensation not perceptibly impaired on trunk, neck, and face. Weakness of muscles of neck and trunk. Partial right sixth palsy, with squint; double facial weakness, with defective articulation; tremor of lips and tongue; weakness of muscles of mastication; dysphagia; partial aphonia. General muscular tenderness to pressure, especially of limbs and abdomen; passive and active movements painful. Acute tenderness of limb nerves. Vision and hearing good; optic fundus normal; pupils reacted well to light and accommodation. Knee-jerks and plantar reflexes abolished; no upper limb jerks; abdominal reflex present. Partial paralysis of diaphragm. No paralysis of sphincters.

Dyspnœa and orthopnœa; respiration rate 26. Pulse 120-170, feeble, slightly irregular. Progressive cardiac dilatation, cyanosis, and hypostatic congestion of lungs. The comparatively slight paralysis of diaphragm did not appear sufficient to account for the rapid cardiac failure. No vomiting. No albuminuria. Constipation. No pigmentation of skin. No suspicion of arsenical poisoning. Patient was conscious up to the time of death, which occurred September 15, eight days after admission to asylum, or six weeks after onset of illness.

Autopsy.

Rigor mortis commencing. Slight excess of fluid in head. Dura mater normal. Very slight pia-arachnoid milkiness over frontal and parietal regions; no adhesion. No appreciable atrophy of convolutions. Brain 42 ozs., fairly well convoluted. No focal lesion. Basal vessels healthy. Heart 8 ozs., pale and greasy; Marchi sections showed slight fatty degeneration in places. No valvular lesion. Blood from jugulars fluid, of a dark laky colour,

contained quantities of *choline*. Lungs normal, save for slight hypostatic congestion of bases. Slight fatty cirrhosis of liver. Kidneys 7 ozs. each, cortex not diminished, capsules not thickened, slightly adherent in places, slight fatty change in renal epithelium. Mucous membrane of stomach vascular and congested, with patches of chronic inflammation and fibrosis. Intestines and other organs healthy.

Microscopical Appearances.

Peripheral Nerves.—No naked-eye changes. Small cutaneous branch to heel, anterior and posterior tibials, ulnar, musculo-spiral and median, examined by Marchi's method, showed intense acute degeneration of nearly all the fibres, with multiplication of their neurilemma nuclei. Both vagi affected, nearly half the fibres giving Marchi reaction. Left phrenic contained a few degenerated fibres. Tibials showed very slight interstitial proliferation commencing in places; none in the other nerves. No vascular or inflammatory changes.

Muscles.—Thenar muscles, triceps, and diaphragm (Marchi) showed acute fatty degeneration of many fibres, with proliferation of their sheath nuclei. Transverse striation preserved. No interstitial overgrowth. Soleus showed rather less fatty change, but some impairment of striation, and a very slight interstitial increase. No naked-eye change.

Vessels of spinal cord congested, otherwise quite normal. No neuroglial, meningeal, or other non-nervous changes.

Anterior horn cells of lumbo-sacral and cervical enlargements (Nissl) show acute changes. Severe chromatolysis commencing in the centre of the cell, and thence involving the whole cell body, with slight swelling and rounding of cell, and atrophy of dendrites. Nucleus swollen, pale, and displaced to the periphery, often bulging out from the side of the cell, though sometimes flattened against it. Nucleolus and membrane stain well, and usually appear normal; the membrane, however, in a few is granular and crumpled in association with extreme nuclear displacement. Actual loss of the nucleus has been searched for in vain; but rupture seems imminent in a few. Some excess of the normal yellow pigment. Nerve cells not invaded by glia cells, or leucocytes. A considerable number of cells of the anterior median group are normal, showing abundance of large stainable masses; these cells are believed to supply the spinal muscles. But all the cells of the other groups, supplying limb muscles are affected

in the manner described; none of these present even an approximately normal appearance. Those of the upper cervical and the dorsal regions are less affected than those of the lumbar and cervical enlargements. Marked changes of the same type are seen in the nuclei of the vagus, hypoglossal and sixth nerves, and the formatio reticularis, in the medulla. The cells of *Clarke's columns*, and also most of the other posterior cornual cells, are normal. The cells of the lumbo-sacral and lower cervical *posterior root ganglia* show similar lesions, very nearly one third of their number showing marked eccentricity of the nucleus, with chromatolysis.

There is degeneration of a very few fibres in the lumbo-sacral anterior and posterior roots.

Posterior columns (Marchi). Extensive degeneration of *exogenous* (posterior root) fibres, visible to naked eye in lumbar sections. No degeneration of cornu-commissural zones at any level, or of Flechsig's central oval area in the lumbar region; these situations are occupied by endogenous fibres; their integrity accords with the normal appearance of the posterior horn cells. Marked degeneration of root fibres in the root-zones, especially at limb levels. In the cervical region, there is much degeneration of the long fibres from lumbo-sacral roots, seen in the neighbourhood of the posterior median septum. Degeneration in funiculus gracilis and cuneatus.

Cerebellar tracts and *restiform bodies* not affected.

Slight degeneration in white matter of *cerebellum*, especially vermis.

Moderate degeneration of *pyramidal tracts*, through their whole extent in the cord, medulla, pons, crura, and internal capsules. In the *anterior limb of the capsule*, more degeneration than in the motor portion; numerous fibres giving Marchi reaction can be traced downwards, backwards, and inwards, into the gray matter of the thalamus.

Cerebral cortex.—Top of each ascending frontal gyrus (Nissl). Some of the Betz cells are normal; but most of them show a central and basal chromatolysis, with nuclear eccentricity, analogous to the anterior horn cell change, and of the kind described in notes of cortex of Case 2, in which the condition is more marked. Apart from slight fatty or pigmentary change, I have searched in vain for changes in the cortical blood-vessels. Marchi-Pal sections show a slight atrophy of *tangential fibres* in places. Marchi sections show a few degenerated fibres in the white matter of the motor convolutions.

CASE 2.—*Sub-acute alcoholic delirium, following fracture of femur, and fatal after ten weeks duration. Advanced fibrotic atrophy of tibial nerves. Vascular degeneration, slight in cortex, but severe in nerves, cord, medulla, and pons, with thromboses and hæmorrhages. Spinal ganglion cell changes and posterior column degeneration. Anterior cornual cell lesion. Degeneration of Clarke's cells and direct cerebellar tracts. Cortical cell lesions, and pyramidal and corticothalamic fibre degeneration.*

C. B., Italian, aged 49, female, married twenty-two years, no children. History of at least eight months excessive indulgence in white wine, brandy and gin; no beer. Had had several attacks of "nerves" (? delirium tremens). On January 26, 1901, fell downstairs while drunk, fracturing neck of left femur; no loss of consciousness. Forty-eight hours afterwards, she developed "delirium tremens," and lay in a state of constant muttering, with hallucinations, seeing cats, dogs, and other imaginary animals, and feeling them bite her; sleeplessness; refusal of solid food; constant craving for alcohol; passed urine and motions under her. Was treated in hospital and in workhouse infirmary, and from the latter was brought to Colney Hatch, on March 2.

On admission to asylum:—Poorly nourished, helpless and bedridden. Perpetually tossing about and throwing off the bed-clothes. No proper sleep. Much incoherent muttering. Paid no attention to questions, or to what went on around her. Once or twice recognised her husband, and asked him for brandy. Hallucinations very persistent—chiefly visual, occasionally pleasant or ludicrous. Repeatedly refused nourishment, and had to be fed by nurse. Action of bladder and bowels always involuntary. Though unable to raise herself in bed, she showed considerable power of resistance to examination; marked rigidity of arms. Elbows, wrists, and knees always flexed. Much coarse tremor of tongue, neck muscles, arms and hands. Legs almost completely paralysed. All muscles much wasted. Upper limb muscles re-acted fairly well to faradism, except triceps, which only responded to strong current. Quadriceps, calf muscles, and tibialis anticus, of both sides, scarcely re-acted to strong faradism. Patient objected to strong current applied to arms, but not to legs. Cutaneous sensation could not be satisfactorily tested owing to mental state; no apparent pains or tenderness. Knee-jerks absent, plantar reflexes lively. Pupils equal, of moderate size, re-action to light sluggish. Accommodation doubtful, owing to mental state and

almost complete defect of attention. Ophthalmoscopic examination unsatisfactory, owing to resistance; no obvious change in discs. Pulse 130, small, compressible, regular. Cardiac sounds weak; otherwise nothing abnormal noted in examination of chest or abdomen. Urine (by catheter) of fair quantity, clear, acid, sp. gr. 1025, albumen in readily recognisable trace. Never any vomiting, or urinous odour of breath. Temperature normal or subnormal, with occasional rise to 99° or 100°.

March 28. Small trophic blisters over right shin and left knee.

March 31. Slight diarrhœa (one day).

April 3. Absolutely "lost" and unresponsive, muttering incoherently. Coarse tremor of arms, more marked, with short series of clonic movements, of 25 vibrations in 5 seconds.

Respiration rose to 44, pulse became almost imperceptible. She lay in a moribund state several days, and died April 6, ten weeks after the accident, the delirium having persisted throughout.

Autopsy.

Rigor mortis present. Emaciated. Healing sores on legs. Bony union of fracture.

Calvaria and dura normal. Excess of subdural and subarachnoid fluid. Slight opacity and thickening of pia-arachnoid over parietal and frontal lobes. Congestion of meningeal veins. Some rounding of convolutions and widening of sulci. Pia stripped fairly readily without tearing cortex. Cerebral vessels apparently healthy.

Lungs. Cavity in right lung, size of an olive; firm localised pleural adhesions at this spot. Some hypostatic congestion of bases.

Heart pale and flabby; left ventricle contracted and empty; whitish clot in right side and in aortic arch; slight atheroma above valves. No valvular lesion. Muscle substance from left ventricle (Marchi, hæmatoxylin) showed intense universal acute fatty change in all the fibres, but scarcely any impairment of transverse striation, and no nuclear proliferation.

Liver deformed, globular, pale; slight nodulation of under surface with thickening of capsule. Marchi and hæmatoxylin sections show a moderate fine cirrhosis of portal distribution, fairly well marked fatty infiltration, and slight fatty degeneration in liver cells; no cloudy change.

Kidneys macroscopically normal on section; very slight adhesion of capsule in places. Marchi and hæmatoxylin-eosin

sections show a good deal of fatty change in the renal epithelium, especially of the medulla; slight thickening of intima and media of some of the arteries; slight interstitial overgrowth beneath capsule.

Peritoneum normal. Stomach apparently normal. Some congestion of jejunum in places; no ulceration. Spleen normal. Chronic thickening of bladder. Uterus and ovaries shrunken.

Brain weighed 40 ozs., heart 10, right lung 13, left 15, liver 36, spleen 2½, and kidneys 4 ozs. each.

Microscopical Examination of Nervous System.

Peripheral Nerves.—Left Posterior Tibial, at ankle (Marchi, hæmatoxylin-eosin), shows very great fibrosis; the nerve bundles are almost entirely converted into dense fibrous tissue permeated by numerous small vessels. There are only a few nerve-fibres left here and there, and many of these give the Marchi reaction. There is thickening of the media and intima of many of the arteries (atheroma); some contain clots, in which focal collections of leucocytes are seen, and organisation appears to be commencing.

Left anterior tibial, in middle of leg, is in a similar condition. The anterior tibial artery shows thickening of the inner coat.

The arm nerves show much less change. Many of the fibres of the left *ulnar* (at wrist) show a cloudy granular appearance of the myelin, without segmentation; a few blackened droplets, but no definite Marchi reaction. No nuclear proliferation, or interstitial overgrowth. The ulnar artery is atheromatous, and contains a small clot commencing to organise. A large clot is also seen in a big vein lying next to it. A small artery in the nerve itself shows general thickening, and contains a clot.

Left musculo-spiral (in lower third of arm) shows slight recent degeneration. Some multiplication of neurilemmal and endoneurial nuclei, with commencing interstitial fibrosis.

Left median (at elbow) shows a few fibres giving definite Marchi reaction of degeneration. There is less nuclear proliferation than in the musculo-spiral. The median at the wrist presents the same appearances as at the elbow.

A few fibres giving the Marchi reaction are seen in the *optic nerves and tracts*.

Anterior horn cells of the cord.—These are much more affected in the lumbar enlargement than in the dorsal and cervical regions. They present the same extreme degrees of central chromatolysis

and nuclear eccentricity that were seen in Case 1. At all levels, the anterior median group supplying muscles of the spine, seems to be nearly as much affected as the others. There is marked general excess of yellow pigment, which, in the lumbar cells, shows a distinct predilection for the periphery of the cell and the bases of the dendrites; in the cervical enlargement, it is more commonly seen as a mass in the midst of the cell. The chromatolysis is seen in many of the cervical cells, but not so marked as in the lumbar region; truly normal examples, however, are scarce.

Cells of posterior horns.—Nearly all these show a similar type of chromatolysis.

The same kind of change is seen in the cells of *Clarke's columns*; none of these appear normal, the great majority are entirely devoid of Nissl-bodies.

In the examination of the cells of the *posterior root ganglia*, the Nissl method was supplemented by Heidenhain's iron-hæmatoxylin. Nuclear eccentricity occurs in only a very few of them; there are no very marked chromolytic changes; there is an excess of pigment, often at the periphery of the cell. In three or four cells in each section, the nucleolus is swollen and intensely stained, while the nucleus is reduced in size, preserves its uniform oval outline, and stains somewhat deeper than normally.

Purkinje's cells of the *cerebellum* show no definite changes. There is slight fibre degeneration in the white matter of the vermis and lateral lobe.

Nissl-sections from several levels of the medulla and pons show in a number of cells of the cranial nerve nuclei, changes similar to those observed in the lumbar anterior horn cells, but more severe.

Cerebral cortex.—Upper parts of ascending frontal and parietal gyri of both sides (formol-paraffin-Nissl). None of the Betz-cells are normal. Their large masses of stainable substance are broken up into a fine powder or granular debris; the parts of the cell thus affected are distinctly paler than they should be. The alteration affects chiefly the central parts of the cell, but may extend to the periphery, in which case the basal part is more affected than the other peripheral regions. Some more or less large masses of stainable substance often persist at the sides and apex of the cell, and on the dendrites, especially the apical process. In association with a chromatolysis of this kind (which, in some few of the cells, is complete) there is observed a displacement of the nucleus to the side or to the upper extremity of the cell. The

nucleus may be swollen and bulging, or may be flattened. The nucleus remains pale, its membrane and nucleolus stain with normal intensity, and the former may be granular. Many of the medium-sized pyramids are beset with glia cells. There is no disarrangement of the cell layers and columns.

Sections prepared by Busch's modification of Marchi's method show numerous degenerated fibres in the white matter of the motor convolutions, and still more in the visual area (right calcarine fissure). There is slight pigmentary change in the minute vessels of the cortex, slight thickening of smaller arteries, and some dilatation of perivascular spaces, but no perivascular infiltration. The vascular changes are trivial compared with those in the cord.

A few degenerated fibres are seen in the part of the *Corpus Callosum* opposite the motor areas.

In the *anterior limb of the Internal Capsule*, numerous degenerated fibres can be seen running downwards, backwards, and inwards, into the gray matter of the thalamus, as in the other cases.

There is considerable degeneration in the *Pyramidal Tracts*, from the internal capsule downwards to the sacral region.

The *Direct Cerebellar Tracts* and *Restiform Bodies* are extensively degenerated.

In the whole cross section of the *Posterior Columns* of the cord there is considerable diffuse degeneration, most evident in the cervical region, and diminishing as the cord is traced downwards. It is also seen in the funiculus gracilis and cuneatus in the medulla. The cornu-commissural zones have not escaped, so that the endogenous fibres appear to be implicated. But the exogenous fibres are more extensively affected; and this is more evident in the lumbar region. In the cervical part the degeneration is most marked in the posterior root fibres, in the root zones, and in Goll's columns near the middle line (situation of long fibres from lumbo-sacral roots). In the upper dorsal levels it is mostly in Goll's columns. In the mid-dorsal region it is more diffuse. At the twelfth dorsal segment it is most marked in the middle of each posterior column; there is less degeneration near the gray matter and median septum. There is not much in the lumbo-sacral region; what there is is chiefly in the root zones. Thus the lesion of the exogenous fibres (derived from posterior roots) appears to preponderate over that of the endogenous fibres.

Nearly all the blood-vessels of the cord are irregularly thickened and tortuous. There is general vascular engorgement.

There are a number of small hæmorrhages in the spinal gray matter; I have not observed any in the white columns. They occur anywhere in the anterior or posterior horn, and are most numerous in the lowest cervical segments; a few are seen in the upper dorsal region, but none lower than this. In sections stained by Van Gieson's method, there is also seen a slight increase of interstitial tissue in Goll's columns in the cervical region, and also in the crossed pyramidal tracts. Amyloid bodies are numerous in the membranes, and in the periphery of the white matter. Thrombi are seen in a few of the larger vessels of the medulla and pons.

Voluntary Muscles (Marchi, hæmatoxylin). Those of the hypothenar eminence show an acute fatty change, affecting different individual fibres selectively, and accompanied by some proliferation of the nuclei of their sheaths. There is no marked interstitial increase, and no appreciable loss of transverse striation, except in a few of the fattiest fibres. A similar condition is seen in the triceps. In the tibialis anticus, the fatty degeneration is less, there is some impairment of striation in places, and a slight interstitial overgrowth. There is thickening of the coats of the small arteries in this muscle.

CASE 3.—*Acute alcoholic mental confusion of "polyneuritic" type. Chronic neuritis. Tuberculosis of lungs. Cortical cell changes. Degeneration of fronto-thalamic fibres, pyramidal tracts, and posterior columns.*

C. K., married woman, aged 45, dressmaker; addicted to beer and spirits several years. Admitted to Colney Hatch, Sept. 8, 1900; duration of mental disorder then stated to have been one week. Short previous attack 3 years ago (not in asylum). On admission, she was emaciated and feeble, and scarcely able to stand; had been refusing her food. Depressed and apathetic; gave irrelevant answers to questions. Had no idea where she was, or how long she had been there. Often thought she was at home; talked of selling her furniture, which she thought she saw in the bare half-padded room where she lay. Once she said, "This is the Hearts of Union Oak." She thought the nurse was her sister. She gave accounts of imaginary journeys she had made "yesterday" or "to-day":—she had been to church, and on her way home slipped and fell, hurting her knee; another time, she had been to Regent Street, to make designs for wall-papers (this she had never done). Thought she was required to get up and do dressmaking jobs, and protested she was unable.

Continually asking all who went near her for beer, gin or brandy; but if asked whether she liked beer she would profess disgust. Very inattentive to questions, or to what went on around. Talkative, mumbling incoherently. Constantly tossing about; had to be placed in padded room to prevent her injuring herself falling out of bed. Passed urine and motions under her.

Fine tremor of tongue, facial muscles and hands. Slight facial weakness, more on right side. All muscles of upper limbs wasted, especially triceps, interossei, and thenar and hypothenar muscles; wrist drop; faradic reaction almost abolished in deltoids, triceps, and small thumb muscles. Muscles of lower limbs flabby and wasted; marked general impairment of faradic excitability. Muscular tenderness, especially of calves, triceps and small thumb muscles. Tenderness of posterior tibial nerves. Knee-jerks absent; plantar reflexes sluggish and feeble. Cutaneous sensation could not be satisfactorily tested, owing to mental state, but there was at any rate no marked analgesia to pin-prick. Pupil reactions normal. Optic discs normal. Pulse 120, regular, feeble. Respiration 30, some cough, signs of consolidation over part of right apex. Evening rise of temperature to 100° or 101°. Became more exhausted and dyspnœic, and had several syncopal attacks, in one of which she died, six days after admission (September 13); conscious up to time of death.

Autopsy.

Rigor mortis present. Skull-cap and dura normal; very slight milkiness of pia-arachnoid over parietal and frontal convexity; no adhesion of membranes; no excess of fluid; practically no wasting of convolutions; brain weighed 42½ ozs.; ependyma of ventricles smooth; no focal lesions; basal vessels healthy. Small amount of caseous tubercle at apex of each lung, some hypostatic congestion of bases. Heart, 7½ ozs.; cardiac muscle pale and friable; some dilatation of right side; valves and aorta healthy. Liver, 42 ozs., soft, fatty, some passive congestion. Kidneys, 5 ozs. each, normal to naked eye; microscopically, very slight interstitial increase. Stomach, intestines, spleen, and pelvic organs, normal.

Microscopical.

Some of the nerves were accidentally spoiled; but the posterior tibial shows a marked fibrotic atrophy, the number of nerve-fibres left being very small; some of these give the Marchi reaction. A few fibres of the median nerve give the Marchi reaction, but otherwise the nerve appears normal.

The anterior horn cells are much less changed than in the other cases; however, there is a general diminution in size of Nissl-granules, and in a fair number of cells there is definite central chromatolysis, with more or less displacement of the nucleus; there is marked excess of pigment. Chromolytic changes are more marked in Clarke's cells. The cranial nerve-cells in the medulla and pons are severely affected with change of the same type as in Cases 1 and 2; extreme displacement of the nucleus, with flattening and crumpling of the membrane. The large cells of the reticular formation are affected in like manner. No definite changes have been made out in Purkinje's cells of the cerebellar cortex; Busch sections of the vermis show numerous degenerated fibres in the white matter; the lateral lobe shows fewer.

Busch's method shows numerous degenerated fibres in the pyramidal system at all levels, in the internal capsule, crura, pons, medulla, and cord; the last was examined at nine different levels. In the anterior limb of the capsule, there are large numbers of degenerated fibres seen running backwards into the thalamus. There is some degeneration of the direct cerebellar tracts.

Of all the columns of the cord, the posterior columns show the most degeneration. In the cervical region it is most marked in Goll's columns bordering each side of the median line, and also in the root zones; there is a slight diffuse degeneration in Burdach's column; the cornu-commissural zones appear to be free. In the dorsal region the degeneration is somewhat diffuse, but is most marked in Goll's columns and in the more posterior parts. In the lumbar region the central oval area of Flechsig escapes, though all around it there is a good deal of degeneration; there is marked degeneration in the posterior root zones, of fibres which have just entered the cord; the cornu-commissural zones are apparently free from degeneration. The lesion is, therefore, mainly an affection of exogenous fibres, as in Cases 1 and 2.

There are no appreciable vascular changes in the brain and cord.

The appearance of the cortex of the paracentral lobule of each side is scarcely distinguishable from that seen in Case 2. There is the same type of Betz-cell change as in the other two cases; none of these giants are normal. There is some excess of satellites about the pyramidal cells, and a slight proliferation of glia nuclei in the deeper layers. There is scarcely any abnormality in the small vessels, and no cell proliferation in their sheaths.

The cardiac muscle shows a distinct nuclear proliferation in the interstices between the fibres.

The diagnosis of neuritis in these cases is established by the microscopical appearances. All three patients were alcoholics. The form of mental disorder in each case is consistent with the view that it and the neuritis were related to the alcoholic condition. Case 1 is an example of an acute polyneuritis of cranial and spinal nerves; in the other two there is found a more chronic form. In the first case there is practically no interstitial or vascular change anywhere in the nervous system; in the third also there is very little. But in the second, vascular changes are severe in the nerves, cord and medulla, and slight in the cerebrum. In Cases 2 and 3, there is advanced fibrotic atrophy of some of the nerves. The table here given may be helpful in presenting concisely the degree and distribution of the various changes. A minus sign signifies "normal," or "no appreciable alteration"; one or more plus signs indicate the presence and degree of change.

	Case 1.	Case 2.	Case 3.
Acute degeneration in nerves	++++	—	—
Fibrosis of tibials	—	++++	++++
Vascular changes in nerves	—	++++	+
,, ,, cord	—	++++	—
Anterior cornual cells:			
Lumbo-sacral	++++	+++	++
Dorsal	++	++	+
Cervical	++++	++	+
Spinal ganglion cells	++++	+	(not examined)
Exogenous fibres of posterior columns:			
Lumbar	++++	++	+
Dorsal	++	++	+
Cervical	+++	+++	+
Posterior horn cells	—	++	—
Endogenous fibres of post. columns:			
Lumbar	—	+	—
Dorsal	—	++	—
Cervical	—	++	—
Cells of Clarke's columns	—	++++	+
Direct cerebellar tracts	—	++++	+
Cells of cranial nerves	++++	+++	+++
Betz cells of cortex	+++	++++	++++
Pyramidal tracts	++	+++	+
Fronto-thalamic fibres	++++	+++	++++

We may proceed to consider the significance of the changes in the brain and cord, in relation to the general

nature of alcoholic paralysis, and in relation to the peripheral neuritis. The whole question is conveniently approached by some preliminary consideration of certain features of the peripheral nerve lesions which have an important bearing on the interpretation of the central changes.

Few pathologists now hold that alcoholic neuritis consists in an inflammatory affection of the nerves. It is essentially a degeneration of the nerve-fibres, as is evident from the study of acute cases, like Case 1, or those reported by H. H. Tooth and by Sidney Martin. In such cases, the appearances resemble those seen in early stages of Wallerian degeneration after nerve section. There is severe acute degeneration of the fibres, in spite of complete (or almost complete) absence of change in the sheaths, connective tissue and vessels. Indeed, the more severe the degeneration, the more striking is the absence of vascular and interstitial changes. These cannot, therefore, be the cause of the fibre degeneration; in those cases in which such changes occur, we must regard them as secondary. For proliferation of neurilemma nuclei and connective tissue-cells, diapedesis of leucocytes, and formation of new fibrous tissue, all appear successively in Wallerian degeneration, and follow as the result of the injury to the nerve-fibres. We may therefore justifiably infer an analogous causation for the similar interstitial changes in sub-acute and chronic neuritis. So far simply as the nerves alone are concerned, the fibre degeneration is the primary element of the neuritic process.

Vascular and interstitial causes of the degeneration being excluded, at least in many acute cases, we might be tempted to ascribe it simply to direct local toxic action on the nerve fibres themselves. But the selective nature of the process is not easily explained as a selection of fibres as such. Apart from the apparent histological similarity of all peripheral fibres, we find that in the various forms of toxic neuritis certain groups of fibres are selected by one poison, and others by another. The selection therefore, cannot be due to local and anatomical factors, since they would be more or less the same for all forms. Though alcoholic neuritis is usually of the "multiple" variety, yet some nerves are

affected more than others. Thus, the motor and sensory paralysis is more marked in the limbs than in the trunk, and more marked in most cases in the distal parts of the limbs than in the proximal parts. This is not adequately explained as the mere result of defective circulation in the extremities, impairing the nutrition of their nerves and so rendering them more vulnerable. Nor is the marked affection of the long nerves, such as the limb nerves, phrenics and vagi, adequately explained by the fact that their fibres have a greater extent of surface exposed to toxines in the blood. For it is not universally true that the longest fibres are the most affected. Thus, one occasionally meets with cases in which the arms are more affected than the legs, or in which the deltoids and glutei are the most affected muscles, as in a case I have in Colney Hatch, which was referred to by Dr. Mott, in his Croonian Lectures. And, in quite analogous fashion, I have more than once found the sensory affection of the extremities less marked distally than proximally, sensation being less impaired on the feet than on the legs.

Moreover, the extensor muscles of the limbs are usually more paralysed than the flexors. This fact cannot be explained by blood stagnation or the length of nerves; nor can it be attributed to stress. The extensors of the legs are perhaps more used than the flexors, as in maintaining the erect posture and in walking. But in the upper extremities the reverse condition holds, for most persons use the flexors of the arms more than the extensors, and the biceps distinctly more than the triceps. Strain, or overwork of certain muscles, may modify distribution of paralysis in certain individuals of special occupations, but cannot account for the typical selective distribution in ordinary cases.

The essential feature of the muscle change is a fatty degeneration, affecting individual fibres somewhat selectively, and independent of interstitial fibrosis. The cross striation is usually unimpaired by the fatty change. The interstitial fibrosis, commonly described as the characteristic muscle change in neuritis, appears to be simply an end-product. The fatty change has not received sufficient recognition. It seems probable that the muscle degeneration is partly the

result of direct toxic action on the muscle substance, and not simply of damage to the nerve supply. If so, the difference of degree of paralysis of extensor and flexor muscles may be partly determined by the physiological differences normally existing between their respective contractile tissues—differences such as those illustrated by Bierfreund's experiments. In whatever way the muscle degeneration is brought about, the limb nerves may suffer more severely than they otherwise would, because they lie in great part of their course in the midst of a large mass of degenerating muscle, and hence are bathed in lymph loaded with deleterious products; the nerves and muscles may thus to some extent be involved in a vicious circle.

But none of the various anatomical and physiological factors I have indicated can fully account for the distribution of any form of toxic neuritis. The distribution varies in type according to the particular poison or toxine at work. There is obviously a far more important principle of selection, of a very special kind, consisting in a particular preference of the individual poison for particular groups of nerve elements. Only in this way can we explain the various localised forms of lead palsy, or the ocular and vagus paralyses in diphtheria. Apart from neuritis, the acute intoxications afford many instances of the characteristic selection of different nervous structures by different poisons. The phenomena of idiosyncrasy show that the selection is characteristic, not only for the individual poison, but also for the individual patient. Susceptibility varies largely according to hereditary and developmental factors, and also according to acquired characters, as is shown in the establishment of tolerance and in other ways.

Such differences of susceptibility can only depend on inherent qualities of the nervous elements. We can scarcely imagine, however, that certain nerve-fibres are picked out by a particular poison on account of any qualities they may possess as mere fibres. For example, we cannot well suppose that lead selects the *fibres* supplying a particular complex group of muscles, and avoids fibres in the immediate neighbourhood going to other muscles or to the skin; for they are

all so similar and similarly situated. The neurone theory, however, affords an intelligible explanation. All the fibres are exposed to the action of the poison or toxine; but particular fibres succumb to it, because their axis cylinders are simply parts of specially susceptible *neurones*, which are subjected, over the whole extent of their cell-bodies and processes, to the all-pervading influence of the poison in the blood. The peculiarities which constitute the basis for special selection by poisons must surely belong to the individuality of the neurone as a whole.[1]

If there should appear to be a selection of the long fibres, it would readily resolve itself into a selection of neurones. For the longer the fibre the more should we expect the trophic influence of the poisoned cell to become inadequate for the maintenance of the remotest parts. If there were simply a selection of fibres as such, we should expect to find more degeneration in the roots and highest parts of the nerves than there is; usually there is little or none. But on the theory of a neuronal affection the facts are explicable: as the poisoned neurone is progressively damaged, the parts which suffer most are those furthest removed from the trophic influence of the cell.

Though local conditions may have an influence (as in diphtheritic paralysis of the palate), yet in all forms of toxic neuritis the distribution forcibly suggests a selective affection of whole neurones. The changes in the brain and cord further support this view. We may pass on to consider, in relation to this question, the changes in the nerve-cells.

[1] It has been thought by some that the validity of the neurone theory, as applied to peripheral nerves, is impugned by the observations of Vulpian, R. Kennedy, and others, on regeneration of nerve-fibres. They have shown that in the distal portion of a divided nerve, though still separated from its central connections, new fibres are developed from the sheaths of the old ones. The question thus arises, whether the peripheral axis cylinder is indeed a part of the spinal cell, as we have been wont to believe. But, at any rate, the fibre and cell are intimately associated both structurally and functionally, and injury to either reacts upon the other. Without committing ourselves on this question, we may yet conveniently retain the word "neurone" as a descriptive term, to embrace the nerve-cell and its processes, with the peripheral fibre in its whole length. For the purpose of the present argument I may, without prejudice, use the word in this sense. The different parts of such a neurone may possess a *limited local autonomy, but the cell is* paramount, and the whole neurone comports itself for the most part as an individual.

The changes in the anterior horn cells have been described by Achard and Soupault, Ballet and Dutil, Dejerine and Thomas, Soukhanoff, Marinesco, Heilbronner, Larkin and Jelliffe, Mott, Wright and Orange. They are well exemplified in my cases. An analogous lesion is seen in the spinal ganglion cells of Case 1 (*cf.* Soukhanoff: Wright and Orange); and a change of the same type affects the Betz cells of the cortex in each case, and also many groups of cells in the pons and medulla. In all these different situations the cell changes conform to the same type. The Nissl-bodies, or large masses of stainable substance, are broken up and reduced to a fine dust, more or less uniformly distributed in the affected parts of the cell, which thus appear faintly and diffusely stained in Nissl-sections. The process of disintegration begins in the middle of the cell, near the nucleus, and thence spreads outwards in every direction, involving the whole cell-body progressively. The last stainable masses to disappear are those on the roots of the dendrites and a few attenuated clumps around the margin of the cell. Simultaneously with this process there occurs a displacement of the nucleus to the periphery.

This form of alteration closely resembles that which section of a nerve trunk produces in the cells of origin of the nerve. It has been called "reaction at a distance," "secondary cell change," or "axonal reaction." Marinesco and others, arguing by analogy, interpret the cell alteration in neuritis as a secondary change set up by the damage to the axis cylinder in the neuritic process.

The objection to this interpretation is, that the cell change in question does not necessarily signify preceding damage to the axon.

For numerous observations show that the same change may occur under conditions in which there is no axis cylinder lesion to produce it. Thus it is seen in the motor cells of the cord (and also in Clarke's cells) after section of posterior roots (Warrington). It is found widely distributed in the nervous system in certain acute diseases, when there are no recognisable axis cylinder lesions, and when the rapidly fatal result renders it improbable that the cells have been so

affected. I may refer to the observations of Ewing and Bonhoeffer on delirium tremens, of Colucci and Worcester on Landry's paralysis, and of C. Bolton on the cells of the vagus nucleus in acute fatal diphtheria. The occurrence of this cell change in acute disease of any kind is very significant, and in none more so than in Landry's paralysis. The pathology of this affection is little understood; but whether it be a separate entity, or only a rapid form of polyneuritis, the significance of the observation is the same. The virulent character of the disease, its strong motor bias, and the appearance of its cell lesions before appreciable fibre degeneration (Worcester) speak strongly against a peripheral initiation. If, however, the disease is identical with polyneuritis, as the researches of Ross and Bury appear to indicate, then their differences become simply differences of degree, and further ground is afforded for the belief that "polyneuritis" depends upon an affection of whole neurones.

The so-called "axonal" type differs from the peripheral chromatolysis seen in the primary lesions of the cell in many acute poisonings, or after artificial elevation of body-temperature, or ligature of the aorta. But such overwhelming experimental injury can scarcely represent the appearances in all the morbid conditions in which the cell is directly affected. It would appear futile to attempt to draw a hard and fast line between primary and secondary affections of the cell; for the neurone being a living organism, there must be a process of interaction constantly going on between all its parts.

Many poisons and toxines, which, if present in a large dose, cause a rapidly fatal result, with a "primary" type of cell change, may, on the other hand, if absorbed in smaller quantities over a sufficient period, apparently set up a neuritis, with a "secondary" type of cell change. But in each case the toxic substance is everywhere distributed in the blood, and is brought to every part of the neurone. It would seem that repeated small doses partially impair the vitality of the whole neurone, leading first to decay of its remotest parts, which then reacts on the cell and so introduces a "secondary" element into the cell affection.

But between the two extreme types, there may be any number of intermediate grades, varying according to acuteness or chronicity of intoxication, or according to differences of resistance of the various portions of the neurone. Though the nerve degeneration in neuritis probably reacts deleteriously on the cells, the changes in the neurones do not begin in their processes. This appears to be clearly demonstrated by the appearances in the sensory neurones.

The spinal ganglion cells show changes of similar type to those in the anterior cornual cells; they are especially severe and conspicuous in the acute Case 1. In addition, there is extensive acute degeneration of their central prolongations in the posterior columns of the cord. In the acute case, the posterior column degeneration appears to affect exclusively the *exogenous* fibres, which enter from the posterior roots, and which, therefore, are processes of spinal ganglion cells. The degeneration is especially severe in those exogenous fibres which are processes of cells in the lower cervical and the lumbo-sacral ganglia, corresponding to the upper and lower extremities respectively. In this case, the posterior column degeneration does not affect the endogenous fibres, or processes of cells in the gray matter of the cord; such fibres are mainly situated in the cornu-commissural zones, and, in the lumbar region, in Flechsig's central oval area. These are normal.

The conspicuously selective affection of the exogenous fibres, especially those from arm and leg roots, clearly shows that the cord lesion represents a degeneration of those same sensory neurones whose peripheral processes are degenerated in the nerves, and whose cells show changes in the corresponding root ganglia. At the same time, very few of their root fibres outside the cord give the Marchi reaction of degeneration; the parts nearest the trophic cells are the least affected.

The view which accords best with these appearances is that which regards the central and peripheral fibre degenerations as simultaneous manifestations of a single disorder of the whole sensory neurone. And, indeed, no other

explanation seems admissible. For what conceivable alternatives have we?

I am not aware that it has even been suggested that the neuritis is secondary to the posterior column degeneration. Such a theory would not only lack evidence, but would appear to be negatived by the fact that section of posterior roots does not produce nerve degeneration. It is equally easy to dispose of the converse theory—that the cord lesion is originated by the nerve lesion. For after section of a nerve, or amputation of a limb, the Marchi method shows no degeneration in the posterior columns; there is only a very slow disuse atrophy. Thus the lesions of central and peripheral prolongations cannot stand to one another in any way in the relation of cause and effect, unless we at the same time postulate an impairment of the resistance of the whole neurone; in other words, a general affection of the neurone.

The only remaining alternative is that the cord lesion is a phenomenon entirely independent of the neuritis. But this would require us to believe that even in uncomplicated typical acute cases, the sensory neurones are damaged by two simultaneous processes, both of which, though quite distinct from one another, yet, by some curious coincidence, have a notable selective preference for the same group of neurones, and even for its particular sub-groups (those of the limbs). This is Heilbronner's view, though he gives no valid reason for such a disregard of the logical injunction against multiplication of causes. He bases his contention mainly on the appearances in the root fibres in his Marchi preparations. Those of the anterior as well as the posterior roots appeared to be degenerated within the cord, but not outside; the change was sharply marked off at the point where they entered or issued from the cord. He therefore thinks that the affection of root fibres within the cord is a separate lesion, *sui generis*. He admits that it cannot be attributed to a meningeal lesion at the point of entrance or exit; for, on the Wallerian principle, that would cause the anterior root fibres to degenerate outside the cord, away from their cells. Moreover, there is no evidence of such

lesion. The crux of the matter lies in the paradoxical appearances in these motor fibres, which gave the Marchi reaction of degeneration in the nerves and within the cord, but were normal in their intermediate parts situated in the roots. That their intermediate portions could remain normal under such circumstances seems incomprehensible, and quite at variance with all we know of their behaviour.

There would appear to be some fallacy in the observation. Heilbronner seems to realise this to some extent, and considers several possible fallacies ; but he overlooks the most probable, which is, that the anterior root fibres in the cord were not really degenerated, but gave the Marchi reaction because of *post-mortem* damage. If the roots are pulled upon in removing the cord from the body, the root fibres outside the cord are protected by their tough external sheath ; but their continuations within the cord have no such protection against stretching, and hence their myelin is damaged. Blackening in Marchi specimens under such circumstances is a familiar observation, and of no pathological import.

But that the degeneration of exogenous fibres is genuine is shown by its systematic distribution over the cross section of the posterior columns at different levels, the long lumbar fibres being degenerated even in the cervical region. Damage by stretching could only extend a short distance into the cord. Thus we can be sure that there is real degeneration of these fibres. But outside the cord they may be better able to preserve their myelin, as there they have primitive sheaths, and are nearer their cells.

By such a process of exclusion of alternatives we are reduced to our first hypothesis, viz., that of a general affection of the whole sensory neurone.

Moreover, the degeneration must begin in the neurone itself, for in many of the severest cases there is no meningeal, interstitial, or vascular change. Yet I would not be thought to undervalue the importance of vascular lesions. In Case 2 there is advanced vascular degeneration, and in the spinal cord there are numerous small hæmorrhages. Such lesions must inevitably cause damage of the nervous

elements. But the exogenous degeneration is more conspicuously selective, and even more intense, in the acute case without vascular lesions, than in the case with vascular lesions. There is, therefore, a selection of these neurones, independent of alteration in their structural environment.

The theory of a general affection of whole neurones is especially supported by severe acute cases, like Case 1; but in the less virulent cases, more opportunity is afforded for the modifying influence of differences in the constitution and environment of the two prolongations of the sensory neurone. They are probably not homologous, and in the peripheral process conduction of impulses is cellulipetal, while in the central it is cellulifugal. There is a more liberal blood-supply in the nerves than in the posterior columns; but blood stagnation in the extremities may render the peripheral process more vulnerable to toxic action, and it seems also more liable to poisoning by products of muscle degeneration. On the other hand, in some cases, the central process is more liable to damage from vascular lesions. The peripheral fibre has a primitive sheath, but the central has not; for this and other reasons, the central fibre has less capacity for repair, if its axon be broken. Waste substances are probably more rapidly removed from the nerves than from the cord; this is, at any rate, true of the products of myelin degeneration which give the Marchi reaction; hence allowance must be made for this fact, in the interpretation of Marchi preparations. And just as clinical experience shows that the neuritic condition admits of improvement, so the microscopical appearances in the nerve-cells and spinal roots show that the affection usually stops short of destruction of the neurone. Therefore, if the axon of either prolongation be only partially impaired, or be able to grow again, its myelin may be restored. In long-standing cases, the appearances may be modified by all these multifarious circumstances, especially if amelioration has taken place. But in acute cases, like Case 1, the morbid process reveals itself as a general affection of the whole neurone. Hence we find a more or less equal degeneration of the central and peripheral prolongations simultaneously, and also a cell change.

The fibre degeneration may perhaps be likened to gangrene of extremities arising in an old man as the result of general impairment of vitality. As this impairment may lead to a symmetrical gangrene of both feet, so the affection of the whole neurone may lead to degeneration of both its prolongations. But just as the gangrene does not necessarily involve the whole limb, so the proximal parts of the neurone may escape actual degeneration; though, as the proximal parts of the affected limb may be in a state of low vitality without actually becoming gangrenous, so it is possible that the myelin of those parts of the fibre nearest the trophic cell may be altered, though not to such an extent as to give the chemical test on which the Marchi reaction depends. Just as the gangrene further impairs the patient's originally feeble state, so the degeneration of the outlying parts of the neurone reacts upon the cell. Moreover in the same way that external injury may determine gangrene in a feeble patient, so unfavourable local conditions may precipitate the onset of degeneration in an already impaired neurone. Also as slight injury may determine gangrene in one or other foot, so any slight unfavourable difference of environment may determine degeneration in one or other prolongation, central or peripheral; so that in some cases (*cf.* Vierordt) the central prolongation of these neurones may be chiefly affected, and in others (*cf.* Marinesco) the peripheral prolongations. But in the same way that the gangrene would not have occurred in a healthy patient, so the fibre degeneration would not have occurred in a healthy neurone. To suppose that the fibre degeneration is the cause of the neurone affection, would be analogous to supposing that gangrene is the cause of senility. Just as many old men present the conditions favourable to the production of gangrene without actually developing it, so, too, many neurones show the characteristic cell change without fibre degeneration; this is seen in many of the cortical neurones (*e.g.* in Case 3). The analogy must not be pushed too far, however, for under appropriate conditions the degenerated fibre may be

restored, though a gangrenous limb can never grow again. Also, I would not be thought to imply that the toxic neuronal affection is actually a premature senility, though the marked excess of pigment in many cells resembles that seen in old age.

Posterior column degenerations in polyneuritis have been described by Vierordt, Korsakow, Kojewnikow, Pal, Biedekarken, Campbell, Soukhanoff, Heilbronner, Wright and Orange, Goldscheider and Moxter, and Marinesco. It seems usual for such lesions to be present; for I can find no record of any case in which the cord was examined by Marchi's method, in which it is stated that the posterior columns were free from degeneration. In Marinesco's case, there was degeneration mainly of endogenous fibres; but with this one exception, an analysis of all the above records shows that the degeneration affected chiefly the exogenous fibres, belonging to peripheral neurones. In my Case 1, the degeneration appears to affect the exogenous fibres exclusively. In Case 2, both systems are affected, but mainly the exogenous. In both cases, the fibres most affected are those derived from the roots connected with the arm and leg. In Case 3, the degeneration is slighter, mainly exogenous.

The occasional affection of the *endogenous* tracts of the cord is not surprising, as the disease evidently affects neurones of many different orders. In Case 2, the lesions of posterior cornual cells and the endogenous fibres in the posterior columns, and the lesions of Clarke's cells and the direct cerebellar tracts, may be partly due to vascular damage. In the light of Warrington's experiments, however, (*vide supra*), one might be tempted perhaps to explain them on van Gehuchten's principle of the reaction of the ganglion cells of a nervous chain upon one another; the secondary spinal afferent neurones might be thus affected because their peripheral stimuli are cut off by reason of the neuritis. But if so, the absence of changes in these secondary neurones in Case 1 is remarkable, unless their development was forestalled by the patient's early death. I am strongly inclined to think that their absence here, and their marked preponderance in

Marinesco's case, point rather to a primary element in the endogenous degenerations, determined by a special susceptibility of these neurones in certain patients.

The affection of the exogenous fibres commonly makes the posterior column degeneration approximate in distribution to that of tabes. This reminds us that cases of alcoholic paralysis have been described, in which ataxic symptoms have been prominent, sometimes overshadowing the neuritic symptoms proper. For such cases, the name "alcoholic pseudo-tabes" has been devised. It is not impossible that in rare instances there may be a difficulty of diagnosis. We may bear in mind that neuritis is typically associated with posterior column degeneration of more or less tabetic distribution, that neuritis may not be conspicuous in its late stages, and also that in true tabes there is often some neuritis as well. Argyll Robertson pupil, however, may probably be regarded as unknown in neuritis, apart from previous syphilis. It was not met with in twenty-eight cases of alcoholic neuritis in which I examined the pupils; nor did any of these exhibit the reverse condition, which Lauder Brunton describes as characteristic of alcoholic neuritis, viz., abolition of contraction to accommodation, with preservation of the light reflex. I might point out, however, that there is very often considerable difficulty in inducing the patient to accommodate for near vision, owing to the defect of attention, which is part of the disease; I have always found that when the patient can be persuaded to accommodate, the pupil contracts normally, except in cases where there is general sluggishness and limitation of all pupillary movements. The pupil condition in most of my cases was normal, confirming the usual description of the text-books. But I have occasionally met with a general sluggishness such as I have alluded to: in one case, the pupils were almost fixed for some weeks, yet recovered perfect movement as the neuritis improved; in this case, the associated mental confusion was profound.

The fact that mental disorder of some sort is almost invariably present in alcoholic polyneuritic cases is evidently of pathological significance, as showing that cortical

neurones are affected. One cannot too strongly insist that this mental disorder is an important part of the disease. Its prominent feature is, in most cases, a pronounced mental confusion, with disorder of observation, and failure of capacity for retaining recent impressions. Hence arises a defect of orientation as to time and place, and loss of memory for recent events, often with illusions as to the identity of persons. The "romancing," illustrated by the pseudo-reminiscences of imaginary journeys, depends probably upon this defect. The disorder was well exemplified in Cases 1 and 3.

The late Prof. Korsakow, of Moscow, showed that the same "polyneuritic psychosis" might occur in neuritis from any toxic cause, though there can be no doubt that alcohol is incomparably the most frequent. During the last three years, I have had under my observation at Colney Hatch fourteen cases of alcoholic neuritis, all with more or less characteristic disorder, without counting Case 2, in which there was a "delirium." And of fourteen other cases which I examined in Poor-Law Infirmaries, all presented marked confusion, and might equally well have been certified as insane. Certification, however, seems to be determined largely by collateral circumstances, such as the number of available beds, or the question whether the patient is in any way troublesome, or is physically fit to be removed to an asylum. The cases met with in the asylum do not differ in any essential respect from those seen outside. But, in both groups, though the defect of attention, memory and orientation is seldom wanting, other features are variable.

The mental disorder is doubtless related in some way to the cortical changes. The striking feature in each of my cases is that the Betz-cells and other large pyramids show the very same type of change as that seen in the anterior cornual cells. With this, there is diffuse, bilaterally symmetrical degeneration of many of their related fibres in the pyramidal tracts. Horizontal sections of the internal capsule show (in addition to degenerated pyramidal fibres) very numerous degenerated fibres in the anterior limb, which disappear in the gray matter of the thalamus; these

apparently connect the thalamus with the motor and frontal cortex, but I have not been able to decide whether they belong to cortical or to thalamic cells. The tangential fibres of the upper motor region were examined in Case 1, and showed a slight degenerative atrophy, as in Jolly's cases.

The combination of this so-called "axonal" cell change with fibre degeneration in the cortical neurones is identical with that seen in the peripheral neurones. Thus, alcoholic neuritis is not peripheral merely, for its characteristic lesion is equally marked in higher neurones which are entirely central. Meyer found a similar condition in eight cases of "delirious and depressive disorders," and speaks of it as "central neuritis." As in his cases, so in mine, the changes in the cortical vessels and neuroglia are very slight, and seem quite insufficient to account for the cell changes. As in his cases also, focal production of the fibre lesions can be excluded absolutely in Cases 1 and 3, and with extreme probability in Case 2. There is clearly a selective affection of neurones. In Cases 2 and 3, the more acute "central neuritis" appears to be superimposed upon an older peripheral neuritis. In Case 1 both are seen in the acute stage together.

Reports of the occurrence of this Betz-cell change (with or without mention of pyramidal tract degeneration) in cases of polyneuritis, appear to be limited to two cases by Faure,[1] one by Turner, and one by Wright and Orange; that it was present in Wright and Orange's case is shown by their diagram rather than by their not very lucid description. To these I would now add my three cases. It seems likely that this cortical change may be common, or usual, in alcoholic neuritis; it has apparently been seldom looked for, as descriptions of cortical cells in this disease are extremely few. The point of interest is that the lesion of cortical neurones is now brought into line with that of peripheral neurones.

The special form of Betz-cell change seen in these

[1] These appear to be the same two cases as those reported by Ballet and Faure.

examples is not confined, however, to cases of definite and pronounced peripheral neuritis, but is also found in other alcoholic, delirious and confusional disorders.

Cases which present, on the clinical side, some form of psychosis, and on the pathological side, an "axonal" Betz-cell change or "central neuritis," appear to group themselves under the following heads:—"Polyneuritic psychosis," with or without recognised peripheral neuritis (Faure, Wright and Orange, Turner), delirium tremens (Ewing, Bonhœffer), various sub-acute delirious conditions (Meyer), confusional states, often with depression (Meyer, Turner, Cauria), and perhaps Landry's paralysis, when associated with cerebral symptoms (Worcester). This list is necessarily imperfect as a classification, for there is considerable overlapping of types. We have to do with a group of closely allied disorders, including many intermediate mixed forms.

Though we are not in a position to state that these are all pathologically identical, we can at any rate say that, in addition to this similarity of microscopical appearances, they present many interesting points of resemblance in their etiology, pathology, symptoms and physical signs. The generalisation thus dimly foreshadowed may prove to be less fantastic than it at first sight appears.

To the demonstration of the similarity of these affections as regards cortical changes, afforded by the researches of those whose names I have given in brackets, I would endeavour here to add a rough outline of some of their miscellaneous clinical resemblances.

Such experience as I have is quite in accordance with Jolly's observation, that a very close relationship exists between the polyneuritic psychosis and delirium tremens. Frequently in cases of marked neuritis there is, in addition to the confusion, a delirious condition, indistinguishable from delirium tremens, with marked tremor and jactitation, and often characteristic visual hallucinations (as in Case 2). In ordinary delirium tremens we find the same marked defect of attention, memory and orientation: Kraepelin mentions the occurrence of pseudo-reminiscences, and delusions as to the identity of persons around: and very

often, as Jolly has observed, at the height of delirium tremens slight neuritic symptoms appear, such as tenderness of muscles to pressure. The neuritic psychosis is often at its onset exactly like delirium tremens, though afterwards it may pass into a condition corresponding more to Korsakow's type; and many neuritic patients whose symptoms in the daytime are mainly confusional, at night are restless and delirious, with auditory or visual hallucinations, the latter being frequently of the same type as those seen in delirium tremens (animals of various kinds, &c.); and there is often a distinct element of fright, or dread, sometimes with delusions of physical torture. It may be difficult to decide whether a given case (*e.g.*, Case 2) is a delirious neuritic psychosis, or a delirium tremens; the question indeed seems little more than a quibble.

In the polyneuritic disorder, as in delirium tremens, there is often marked defect of co-ordination and equilibration; and each of my three cases shows a degeneration in the white matter of the cerebellum, especially of the vermis, similar to that which Bonhœffer found in delirium tremens. As also in some of the cases of delirium tremens which Bonhœffer has described, so, in the neuritic cases, one not infrequently observes symptoms suggestive of focal lesion of particular cortical areas, yet without any macroscopic meningeal or vascular change. These symptoms, though severe at the time, often pass off so rapidly and completely, that the diagnosis of gross lesion is soon shown to be erroneous. Thus, in the second week of my Case 1, there was a condition of coma with hemiplegia, corresponding to which the pathological examination revealed nothing. Coma was complete for forty-eight hours; the hemiplegia gradually passed off in the course of the next eight days. In Case 2, one might perhaps at times have been inclined to suspect some lesion of the visual area; if one made a feint to strike the patient, there was not even a reflex closure of the lids, though her eyes were wide open, and she was talking at the time; the head and eyes were nearly always turned towards the left, especially when the visual hallucinations were active. As in delirium tremens, irregular

jactitation, and also rhythmical convulsive clonic jerking of the limbs, of a somewhat significantly epileptiform type, are frequently observed in polyneuritic cases, as in Cases 1 and 2, and, to a less extent, in 3. These irritation-phenomena are doubtless of cortical origin.

There is an overlapping of types, not only between delirium tremens and the neuritic psychosis, but also between each of these and the other disorders I have mentioned.

Alteration of the reflexes is common in all, but varies according as the cortical or the peripheral lesions predominate; if the former, then rigidity of the limbs may also be observed.

Meyer thus sums up the clinical features in his eight cases of "central neuritis": "After a course in which there is no suspicion of organic disorder, there appears, more or less suddenly, difficulty of locomotion, increasing weakness for co-ordinated movements, at times jactitations of the limbs, and rigidity, and disorders of the reflexes, often together with diarrhœa and occasional febrile fluctuations; the mental condition is either that of anxious perplexed agitation, delirium, or stupor, similar to a protracted delirium tremens." There was evident defect of orientation in his Cases 2, 3, 5, 7, 8, doubtful in Case 1, and none was made out in Cases 4 and 6. An alcoholic history was present in Cases 5 and 8, denied in Case 7, while as to the others there is no statement. There was a history of lead-poisoning in Cases 4 and 6, which is somewhat significant in view of the well-known tendency of lead to induce neuritis. Many features of Meyer's cases suggest some form of toxæmia.

It is interesting to compare my Case 2 with these examples. The patient, as the result of a fracture, developed within a few hours what appeared to be a delirium tremens, with the usual tremor, excitement, and tactile and visual hallucinations of cats, dogs, &c. But instead of terminating in the usual way in rapid recovery or death, the condition was protracted for ten weeks, and there were observed the same rigidity of the arms, obstinate refusal of food, and slight diarrhœa before death, as were presented by

Meyer's cases; while, in addition, there was polyneuritis, and the spontaneous clonic movements of the limbs so frequently seen in polyneuritic conditions.

In all these various disorders—delirium tremens, neuritic psychosis, confusional insanity, &c.—in addition to the defect of memory and orientation, the pseudo-reminiscences, visual hallucinations, excitement, tremor, speech disorder, jactitation, rigidity, alteration of the reflexes, and so forth, there may be also hallucinations of threatening voices, delusions that food is poisoned, obstinate refusal of food (as in my Cases 2 and 3), and delusions of physical persecution and torture. In all these conditions there is frequently also marked depression, almost deserving the name of melancholia.

It may be observed in passing that in Korsakow's type of neuritic psychosis, the melancholic factor is sometimes incidentally illustrated in a curious way by the romancing. I have several times noticed that the imaginary journeys have been either fruitless, or attended by some mishap, such as a fall (*cf.* Case 3) or sudden illness, or a fright from a runaway horse; or the patient tells us that she found her mother very ill; or she sends her little girl to fetch the supper beer, but the child drops the jug as she is bringing it home. The pseudo-reminiscence of these imaginary misfortunes is the occasion for tears.

With regard to confusional insanity, it may be pointed out that Korsakow's "polyneuritic psychosis" is really a marked form of confusional disorder. Meyer's "delirious and depressive" cases are closely allied, not only to delirium tremens, but also to the neuritic psychosis and confusional insanity. He does not appear to have examined any of the nerves in his cases. In my experience, slight neuritis is not very uncommon in alcoholic confusional states, but it requires to be systematically looked for. In Cases 2 and 3, it was by no means obvious clinically, though there was extreme atrophy of the tibial nerves.

As to Landry's paralysis, I would simply remark that in Worcester's case there were somewhat analogous mental symptoms, and also that Ross and Bury have shown that,

as regards the peripheral affection, no hard and fast line can be drawn between Landry's paralysis and polyneuritis.

Jolly's observations show that in some cases of neuritis the mental disorder may be very slight (possibly, even, altogether absent), and that, on the other hand, Korsakow's polyneuritic psychosis may occasionally occur without definite peripheral neuritis. Side by side with this may be set the pathological observation of the occurrence of this neuritic lesion of cortical neurones in certain cases apart from recognised peripheral neuritis; to Meyer's cases, and those he quotes, may now be added those of Cauria. There is no doubt that in certain patients the cortical neurones are the more vulnerable, and in others the peripheral. Our conception of neuritis must be widened, and not restricted to so-called typical cases. The selective action of the toxic agent (whatever it be) is clearly modified by differences of resistance of the various neurone systems, depending largely on hereditary and developmental factors, and the occupation and habits of the patient. Even in mere drunkenness, one man's liquor flies to his head, and another's to his legs.

We have seen that the neuritic, delirious and confusional conditions displaying this characteristic cortical change present numerous clinical resemblances. They also have much in common as regards their etiology.

Neither polyneuritis, delirium tremens, nor the confusional disorders can be regarded as the expression of a mere alcohol-poisoning. They have a more complex etiology, and present the characters of a severe general disease, of the nature of a toxæmia, depending probably on an auto-intoxication from disordered metabolism. They may, most of them, result from other poisons besides alcohol, though their appearance is evidently favoured in a very special way by chronic alcoholism. But they only result indirectly from the alcoholism, and require the co-operation of various contributory or exciting causes, such as shock, surgical injury, chill, pneumonia, tuberculosis and other febrile and afebrile illnesses, want of food, the onset of the menopause, &c.; Judson Bury mentions cases of polyneuritis following injury

to the head. The patient may have been addicted for years to alcohol, but the introduction of one of these additional factors suddenly gives rise for the first time to one or other of these disorders.

Moreover, all of them, but especially neuritis and delirium tremens, present a series of features directly suggestive of an auto-toxic origin. Not only do we see that many of their contributory causes are of a kind eminently calculated to cause derangement of metabolism, but we cannot fail to note the frequent occurrence of circulatory disturbance, rapid pulse, acute fatty degeneration of the heart and skeletal muscles, pyrexia without recognisable cause, profuse paroxysmal sweats even in afebrile cases, albuminuria, and sometimes diarrhœa as the end approaches; while, at least in delirium tremens, there is an alteration of the blood-count, with increase of polynuclear leucocytes, and diminution of eosinophile cells (Elsholz). All these phenomena are strongly suggestive of a severe toxæmia; and so also, I think, are many of the nervous manifestations—such as the various sensory disturbances, the motor weakness, tremor, inco-ordination, giddiness, speech disorder, twitchings of muscles, and epileptiform convulsions. Jolly has pointed out the toxic significance of many of these, both in delirium tremens and in neuritis. They remind us of the analogous symptoms seen in acute alcohol-intoxication. Similar suggestive features are far from uncommon in many other delirious and confusional states.

The frequent chronic gastritis, and the fatty, cirrhotic, and other disorders of the liver and kidneys, may be etiologically important. Cirrhosis of the liver, however, was very slight in two of my cases, and absent in the third, supporting the generally accepted opinion that marked cirrhosis is uncommon in neuritis, and perhaps also suggesting that the toxæmia does not set up neuritis unless at the same time there is nervous instability. Beer was a factor in Case 3, but not in the other two; the cases I have seen do not support the theory that arsenic is always a factor in alcoholic neuritis, but rather suggest that spirits are an important cause. This is consistent with the auto-intoxica-

tion theory, inasmuch as it seems to add weight to the gastro-intestinal and hepatic affections. The choline present in the blood in great quantity in Case 1 is, of course, of no etiological significance; it simply indicates the great amount of myelin degeneration in progress at the time of death.

The fact that the so-called "axonal" Betz-cell change is seen in acute forms, like delirium tremens, is opposed to the view that it is secondary to an axis-cylinder affection. And in my Case 3, as in some of the cases of Meyer and Faure, though the pyramidal tract degeneration was comparatively slight, *all* the Betz-cells showed this change. In the acute cases the cell changes far outweigh the fibre degeneration; the latter appears to be simply a secondary manifestation of the disorder of the neurone. The cell changes are almost certainly primary. In some of Bonhœffer's cases the changes in many cells showed characters approaching those of Nissl's "acute alteration," which is good evidence of a primary affection. In other delirious cases clinically indistinguishable, he found a much more definite "axonal" type; his description[1] would apply accurately to the cells in my neuritic cases, and so also would Ewing's.

In all these varieties of nervous disease occuring in alcoholic patients, the affected neurones, central and peripheral, present the same essential lesion—a cell change of distinct type, with or without degeneration of the myelin sheath of the parts most remote from the cell. The changes in the neurone do not begin in the prolongations, but express a disorder which leads to such general impairment of the whole neurone, that the parts furthest from the trophic centre degenerate. The affection is polyneuronal rather than polyneuritic. In all forms, we have to do with a general toxæmia, affecting whole neurones of many different orders throughout the nervous system, and rarely or never affecting peripheral neurones only. In some cases the peripheral neurones are the more vulnerable, in others

[1] "Die grossen Pyramiden; der Zell-leib nicht gleichmässig tingiert; einzelne fast ganz farblose Stellen; die farbbäre Substanz zeigt in einzelnen Zellen noch Reste der parallelen Anordung; namentlich in der Peripherie sind zahlreiche grabkörnige Partikelchen; die Fortsätze sind nicht abnorm lang; der Kern ist wandständig, gross, blass."

the central. Hence in some cases the "peripheral neuritis" predominates, in others the "central neuritis." Thus the physical illness is closely related to a number of affections which come within the province of the alienist. The typical case of severe peripheral neuritis, familiar in the hospital ward, is connected by any number of intermediate mixed forms, with several varieties of confusional insanity, delirium, and allied disorders, in which there may be no appreciable peripheral affection.

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